Case Control Study

The Role of Autonomic Function in Exercise-induced Endogenous Analgesia: A Case-control Study in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome and Healthy People

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Background: Patients with myalgic encephalomyelitis / chronic fatigue syndrome (ME/CFS) are unable to activate brain-orchestrated endogenous analgesia (or descending inhibition) in response to exercise. This physiological impairment is currently regarded as one factor explaining post-exertional malaise in these patients. Autonomic dysfunction is also a feature of ME/CFS.

Objectives: This study aims to examine the role of the autonomic nervous system in exercise-induced analgesia in healthy people and those with ME/CFS, by studying the recovery of autonomic parameters following aerobic exercise and the relation to changes in self-reported pain intensity.

Study Design: A controlled experimental study.

Setting: The study was conducted at the Human Physiology lab of the Vrije Universiteit Brussel.

Methods: Twenty women with ME/CFS- and 20 healthy, sedentary controls performed a submaximal bicycle exercise test known as the Aerobic Power Index with continuous cardiorespiratory monitoring. Before and after the exercise, measures of autonomic function (i.e., heart rate variability, blood pressure, and respiration rate) were performed continuously for 10 minutes and self-reported pain levels were registered. The relation between autonomous parameters and self-reported pain parameters was examined using correlation analysis.

Results: Some relationships of moderate strength between autonomic and pain measures were found. The change (post-exercise minus pre-exercise score) in pain severity was correlated (r = .580, *P* = .007) with the change in diastolic blood pressure in the healthy group. In the ME/CFS group, positive correlations between the changes in pain severity and low frequency (r = .552, *P* = .014), and between the changes in bodily pain and diastolic blood pressure (r = .472, *P* = .036), were seen. In addition, in ME/CHFS the change in headache severity was inversely correlated (r = -.480, *P* = .038) with the change in high frequency heart rate variability.

Limitations: Based on the cross-sectional design of the study, no firm conclusions can be drawn on the causality of the relations.

Conclusions: Reduced parasympathetic reactivation during recovery from exercise is associated with the dysfunctional exercise-induced analgesia in ME/CFS. Poor recovery of diastolic blood pressure in response to exercise, with blood pressure remaining elevated, is associated with reductions of pain following exercise in ME/CFS, suggesting a role for the arterial baroreceptors in explaining dysfunctional exercise-induced analgesia in ME/CFS patients.

Key words: Aerobic exercise, aerobic power index, autonomic nervous system, exercise-induced analgesia, exercise-induced hypoalgesia, fibromyalgia, heart rate variability, stress-induced analgesia, pain

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It has been reported that aerobic exercise causes an acute analgesic effect in healthy people (1,2). Increased pain thresholds and pain tolerance, as well as lower pain ratings, have been found to occur following exercise (3). Depending on the exercise intensity and duration these reductions in pain perception can last up to 30 minutes post-exercise (1). Patients with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), a condition characterized by severe fatigue, widespread pain, cognitive impairments, and delayed recovery following exercise (4-6), are unable to activate brain-orchestrated endogenous analgesia (or descending inhibition) in response to exercise (7-9). This physiological impairment is currently regarded as one factor explaining post-exertional malaise in these patients.

At present, the precise mechanisms of this stress or exercise-induced analgesia (EIA) are unknown. It has been hypothesized that the cardiovascular and the hormonal system could be responsible for this mechanism. This comes as no surprise as it is well known that the sympathetic branch of the autonomic nervous system and the hypothalamic-pituitary-adrenal axis (HPA-axis) are activated during exercise and that there is a mutual stimulatory interaction between these 2 systems (10,11). (Nor)adrenaline and cortisol are major end products of the sympathetic nervous system and the HPA-axis, respectively. In addition to their effects as stress hormones, they have strong analgesic effects in the central nervous system (i.e., as brain neurotransmitters and acting on the dorsal horn neurons) (12).

Many studies have examined the possible interaction between the cardiovascular system and exercise-induced changes in pain. Exercise is accompanied with dynamic changes in cardiac responses which result in an increased blood flow and a redistribution of the blood to satisfy the energy demands of the working muscles. These cardiodynamic changes are induced by sympathetic activation and parasympathetic withdrawal (13). It is thought that the increases in heart rate and blood pressure during exercise will activate the arterial baroreceptors, which is associated with the release of pain relieving neurotransmitters and peptides and the activation of pain modulatory regions in the brain (14-16). This hypothesis is based on observations from animal studies, and there is no direct and conclusive evidence for this theory in humans.

It has also been reported that through blood pressure increases, growth hormones and β-endorphins are released by the HPA-axis which in turn will activate opioid receptors and lead to analgesia (17). However previous studies were not able to confirm this theory (18,19). But there is evidence supporting the role of the hormonal system in EIA as observed in humans. It has been shown that during aerobic exercise the release of adrenocorticotropic hormone (ACTH) increases, and that this is associated with increased dental pain thresholds (20). When the release of ACTH during exercise is experimentally limited, this also limits the magnitude of pain threshold increases. As hormones such as ACTH are released by the HPA-axis, it seems that this physiological stress system plays an important role in the phenomenon of EIA. Furthermore, in order to recover from exercise and restore homeostasis, the HPA-axis will be activated, which results in increased post-exercise cortisol production and enhanced vagal activity to restore the balance between the sympathetic and parasympathetic nervous system (21).

While the role of the hormonal system in EIA has been previously studied by determining hormone concentrations in saliva and blood samples, to our knowledge, no studies have examined the relationship between exercise-induced changes in pain and autonomic function. This would be of particular relevance for unraveling the dysfunctional EIA in ME/CFS. Autonomic dysfunction is an established feature of ME/CFS (22-24) and has been linked repeatedly to the inability of ME/CFS-patients to perform or recover from exercise/physical activity (9,25,26). Hence, the purpose of this study was to examine the role of autonomic function in EIA in healthy sedentary (HS) controls and ME/CFS patients. It was hypothesized that in healthy people the sympatho/vagal balance would have been restored during recovery from exercise, while this would not be the case in ME/CFS, and that this ability to recover from exercise would be associated with the degree of EIA.

Methods

Participants

Twenty HS women and 20 women with ME/CFS participated in this study. Patients diagnosed with ME/CFS following the 1994 Center for Disease Control and Prevention criteria (27) were recruited from the patient databases from the department of internal medicine at a university hospital, and from a private practice for internal medicine. The HS group was a convenience sample consisting of healthy friends and relatives from the ME/CFS patients and volunteers who replied to ad-

vertisements. Healthy volunteers with a medical history of endocrine, immune, cardiovascular, or autonomic abnormalities were excluded. Sedentary was defined as having a seated occupation and performing ≤ 3 hours of moderate physical activity/week (28). To prevent sources of bias or confounding factors 1) only women, 2) aged between 18 and 65 years old, 3) who were not pregnant, lactating, or > 1 year postnatal were included, and 4) participants were asked to refrain from consuming caffeine, alcohol, nicotine, and physical exertion on the day of the experiments, 5) ME/CFS patients were asked (if medically permissible) to abstain from medication acting on the cardiovascular system on the day of the experiments and from medication acting on the central nervous or hormonal systems at least 48 hours prior to the experiments.

An a priori sample size calculation was based on a similar study (29) which evaluated autonomic dysfunction in response to a submaximal bicycle exercise test in women with chronic stroke, as no studies in ME/CFS were available, and on a study (9) which used a submaximal bicycle exercise test to evaluate EIA in women with ME/CFS. The calculations revealed that 16 to 21 participants/group were required to obtain a power of .80 with α = .05.

All participants took part in a familiarization session and an experimental session.

Familiarization Session

All procedures were approved by the local Ethics Committee of the University Hospital Brussels/Vrije Universiteit, and participants provided informed consent at the familiarization session. Participants filled out a questionnaire to collect sociodemographic/disease related information and the Hospital Anxiety and Depression Scale (HADS) (30). One of the researchers (JVO) measured participants' weight and height, and although not an inclusion criterion, it was examined whether the included patients also fulfilled the more recent Canadian criteria for ME/CFS (31), which was the case for all patients. To prevent stress on the day of the experiment due to the unfamiliar environment, each participant was guided through the lab, the full test procedure was explained, and the different assessment methods and materials were shown and tried out. Prior to leaving, an accelerometer (Actical, Mini Mitter, USA) was attached to the wrist of the non-dominant hand and participants were asked to wear it continuously for at least 6 full days to measure their daily activity levels (32-34). The second visit was scheduled to take place within a range of 7 – 21 days following the first visit. The procedures are summarized in Fig. 1.

Experimental Session

The experiments took place in an acclimatized room with at constant ambient temperature between 21 and 23°C.

Exercise Testing

The Aerobic Power Index is a standardized reliable and valid submaximal exercise test for both ME/CFS patients and HS people and has been previously used to document the lack/presence of EIA in these populations (9,35,36). The test was performed as described in

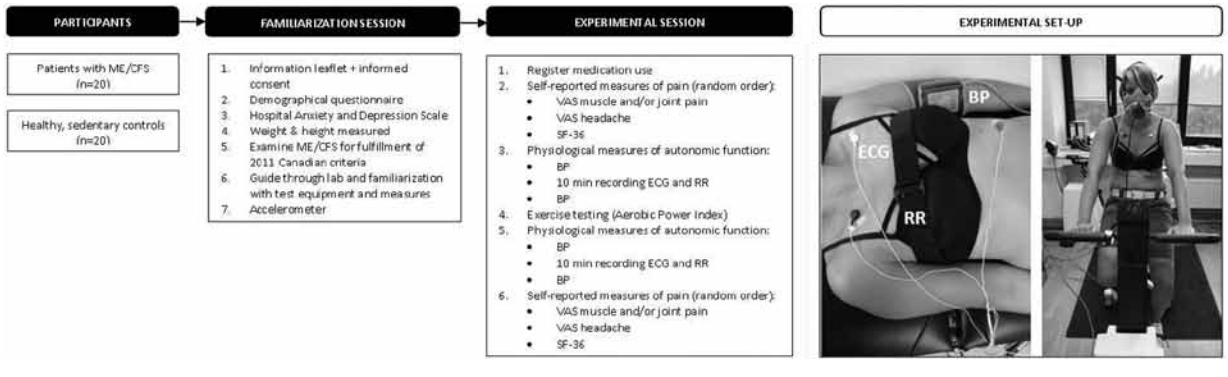

Fig. 1. *Schematic of the experimental procedures.*
ECG: electrocardiogram, RR: respiratory rate, BP: blood pressure

our previous study (9). In summary, cycling started at a workload of 25 watt (W)/minute and a pedaling rate of 70 rotations/minute, and linearly increased with 25 W/minute until 75% of the age predicted maximal heart rate (HR) was achieved (37).

Continuous cardiorespiratory monitoring was performed using a portable cardiopulmonary indirect breath-by-breath calorimetry system (MetaMax 3B, Cortex Biophysik, Germany) and electrocardiographic (ECG) sensors connected to the Nexus-10 system (Mind Media BV, The Netherlands).

Immediately following the exercise test, the mask was removed and the participant was asked to rate their perceived exertion (RPE) using the Borg scale (39).

Physiological Measures of Autonomic Function

Prior to exercise testing (at rest) and during the subsequent recovery period, physiological measures of autonomic function were performed. Autonomic modulation of HR variability and respiration rate were measured using the Nexus-10 wireless and portable telemetry data acquisition system and analyzed offline with the BioSig toolbox in MATLAB software (The MathWorks, USA). Measures were taken continuously during 10 minutes of quiet supine lying, and the means of these 10 minute periods were calculated and used for further analysis.

ECG was performed to measure HR variability (HRV). The root mean square of successive differences between the beat-to-beat or NN intervals (RMSSD) was calculated. Frequency analysis of HRV was performed using the quotient (HRV LF/HF ratio) of low-frequency components (i.e., the power in the low frequency [LF] range between 0.04 – 0.15Hz) over high-frequency components (i.e., the power in the high frequency [HF] range between 0.15 – 0.40Hz) after fast Fourier transformation (39,40).

Respiration rate (RR) was measured with an elastic belt which was placed around the chest (Fig. 1) and included a piezoelectric sensor responsive to stretch. Peak detection was applied, and the RR was defined as the number of peaks per minute.

Blood pressure (BP) was measured at the start and at the end of the 10 minute periods preceding and following the exercise test using an electronic BP monitor (Bosi medicus, BOSCH + SOHN GHMB U.CO.KG, Germany). The inflatable cuff was placed around the left upper arm, which was supported and positioned at heart level.

Self-reported Measures of Pain

EIA was assessed using self-reported pain measures, which were presented in random order to the participants prior to and following the exercise test and the autonomic measures.

Pain (muscle and/or joint pain) and headache intensity were assessed using a visual analogue scales (VAS). A VAS is a continuous scale comprised of a horizontal line which measures 100 mm with the left outer end labeled as no pain or headache at all and the right outer end labeled as unbearable pain or headache. The VAS is the most commonly used tool to evaluate pain (41).

The SF-36 bodily pain subscale consists of 2 items which assess bodily pain intensity and interference of pain with normal activities (41). A score between 0 – 100 is obtained on the subscale, and a higher score indicates lack of bodily pain. The SF-36 is reliable and valid in a wide variety of patient populations (42-44) and appears to be the most frequently used measure in ME/CFS research (45).

Statistical Analysis

Statistical analyses were conducted using SPSS version 20.0 (IBM Corporation, USA) and the significance level was set at .05. Descriptives were calculated and normality of the data was evaluated using the Shapiro-Wilk test and visual assessment of the histograms, QQ-plots, and boxplots. When possible outliers were identified using this method, it was examined whether these were in the normal range of the according measures or whether they were considered as outliers using the outlier labeling rule (46).

Comparability of the groups at baseline and regarding exercise response was examined using the Independent Samples T test or the Mann-Whitney U test. The Fisher exact test or the Pearson Chi-Square test was used to analyze binary and categorical data. A linear mixed model analysis with 2 factors, i.e., group (ME/CFS vs. HS) and time (day 1, day 2, day 3, day 4, day 5, day 6), was conducted to examine potential differences regarding daily physical activity levels. When required, post-hoc comparisons were made and adjusted using the Bonferroni-correction.

For each group (ME⁄CFS and HS) possible differences in the response of each of the outcome measures to exercise was examined using the Paired Samples T test or the Wilcoxon Signed Rank test.

The changes in self-reported measures of pain and outcome measures of autonomic function in response to the exercise were calculated (Δ = post-exercise minus

pre-exercise scores), and bivariate Spearman and Pearson correlation analyses were performed to examine the relationship between autonomic function and EIA.

Results

Participants

Sociodemographic characteristics were comparable between groups as shown in Table 1. HADS scores indicated that there were no significant group differences regarding levels of anxiety, while the ME/CFS patients reported significantly higher levels of depression than HS participants.

The mean time from diagnosis reported by the patients was 70.3 months (ranging from 1 to 162 months, median 63.5 months). Even though participants were asked to refrain from central acting medication on the day of exercise testing, 6 ME/CFS patients and one HS participant reported using medication. However, only 2 ME/CFS patients took central acting selective serotonin reuptake inhibitors, while all other participants took peripheral acting drugs including paracetamol, diclof-

Table 1. *Demographic baseline characteristics.*

	CFS/ME group (n=20)	HS group (n=20)	Between group comparison (*P*-value)
Age, years			.155
Mean (SD)	41.6 (9.8)	34.6 (15.2)	
BMI			.245
Mean (SD)	26 (6)	24 (4)	
Activity levels, AC			.083
Mean AC day 1 (SD)	275 (31)	320 (30)	
Mean AC day 2 (SD)	222 (31)	322 (30)	
Mean AC day 3 (SD)	220 (31)	368 (30)	
Mean AC day 4 (SD)	239 (31)	335 (30)	
Mean AC day 5 (SD)	221 (31)	342 (30)	
Mean AC day 6 (SD)	218 (31)	318 (31)	
Mean AC over 6 days (SD)	233 (27)	334 (26)	.010
Employment status			.127
Student (n)	1	7	
Retired (n)	0	1	
Full-time (n)	4	2	
Part-time (n)	6	4	
Non-employed (n)	9	6	
Years of education			.177
Mean (SD)	14.4 (2.8)	15.6 (2.7)	
Highest degree of education			.054
Primary school (n)	0	0	
Secondary education (n)	12	5	
Higher education - university or college (n)	8	15	
Higher education - adult education social Advancement course (n)	0	0	
Marital status			.609
Single (n)	9	12	
Living together (n)	2	1	
Married (n)	8	7	
Widow (n)	1	0	
Children			
Yes	7	12	.205
No	13	8	
Mean number (SD)	1.1 (1.0)	1.0 (1.3)	.601
HADS, score			
Anxiety, mean (SD)	11.2 (5.6)	9.1 (7.2)	.180
Depression, mean (SD)	10.7 (5.3)	6.2 (6.6)	.023

ME/CFS, Myalgic Encephalomyelitis / Chronic Fatigue Syndrome (ME/CFS). HS, healthy sedentary. SD, standard deviation. n, number of. AC, activity counts.

enac, and non-steroid anti-inflammatory drugs which were allowed. Nevertheless, there were no significant between group (P = .091) differences regarding medication use.

No significant group differences were found regarding daily physical activity levels or possible day-to-day fluctuations (time*group P = .083). When the mean activity counts over 6 days were compared, ME/CFS patients were significantly less active compared with HS controls (P = .010). However, this did not affect exercise performance or exercise capacity, as there were no significant group differences regarding these outcome measures.

Group Differences and Exercise Response

All participants were able to complete the exercise test, and there were no significant differences between the groups regarding theoretical target HR (P = .149, ME/CFS 134 ± 7 bpm, HS 140 ± 12 bpm), actual achieved peak HR (P = .453, ME/CFS 140 ± 9 bpm, HS 142 ± 10 bpm), actual achieved mean HR (P = .092, ME/CFS 114 ± 10 bpm, HS 119 ± 10 bpm), cycling time (P = .401, ME/CFS 3.86 ± 1 min, HS 4.15 ± 1.15 min), maximum workload achieved (P = .327, ME/CFS 109 ± 25 W, HS 118 ± 25 W), mean peak oxygen uptake (VO2peak) (P = .112, ME/CFS 16.98 ± 4.25 mL/min/kg, HS 19.96 ± 6.80 mL/min/kg), mean peak ventilation (VEpeak) (P = .758, ME/CFS 31.81 ± 9.67 l/min, HS 31.61 ± 11.30 l/min), and peak respiratory exchange ratio (RERpeak) (P = .101, ME/CFS .76 ± .89, HS .72 ± .08). Although both groups performed a similar exercise test and showed similar exercise capacity, the average exercise load was perceived as "somewhat hard" by the HS group (RPE 12 ± 2) and "very heavy" (RPE 16 ± 3) by the ME/CFS patients (between group P < .001).

Results of self-reported measures of pain are shown in Table 2. All these outcome measures indicated the presence of significantly higher pain complaints in the ME/CFS group compared to the HS group at baseline as well as following exercise. In the HS group the VAS scores for pain and headache decreased in response to the exercise test, and the SF-36 bodily pain score increased, indicating that less pain complaints were experienced following exercise. However, only for VAS pain was the decrease large enough to reach significance. In the ME/CFS group no significant changes were established. Comparing the Δ between groups confirmed previous observations of dysfunctional EIA (VAS pain P = .015, VAS headache P = .659, SF-36 bodily pain P = .758).

Results regarding within and between group changes in autonomic parameters are presented in Table 2. At baseline, BP, RR, and cardiac parameters in the time-domain were not significantly different between groups. Frequency-domain parameters LF and HF were significantly lower in the ME/CFS group compared to the HS group. The LF/HF ratio was similar between groups. In the HS group mean HR, RMSSD, HF, and LF/HF ratio did not significantly change following exercise, while LF significantly decreased. The ME/CFS group showed a significantly higher HR and lower HF following exercise, while RMSSD, LF, and LF/HF ratio remained unchanged. Both groups had higher RR following exercise and their systolic BP increased while diastolic BP remained stable. After 10 minutes of supine recovery, both systolic and diastolic BP were similar to the values seen at rest. There were no significant group differences regarding Δ (P < .05). Following exercise, there were no group differences regarding BP, RR, or mean HR. Significantly lower RMSSD, LF, and HF values, and a higher LF/HF ratio were seen post-exercise in the ME/CFS group compared to the HS group.

Correlation Analyses

As displayed in Table 3, Δ VAS pain was strongly correlated with Δ diastolic BP in the HS group. In the ME/CFS group, strong positive correlations between the Δ VAS pain and Δ LF, and between Δ SF-36 bodily pain and Δ diastolic BP, were seen. In addition, Δ VAS headache had a strong, inverse relationship with Δ HF.

Discussion

This is the first study examining the role of autonomic (dys)function in EIA. The dysfunctional EIA in the ME/CFS group was shown to be associated with reduced parasympathetic reactivation during recovery from exercise. In addition, poor recovery of diastolic BP in response to exercise, with BP remaining elevated, was associated with reductions of pain following exercise. The latter finding suggests a role for the arterial baroreceptors in explaining dysfunctional EIA in ME/CFS patients.

We hypothesized that in healthy people the sympatho/vagal balance would have been restored during recovery from exercise, which was the case for all autonomous parameters except LF. Although LF was not fully restored to pre-exercise values, the magnitude of (para)sympathetic activity cannot be as easily isolated from LF. The LF/HR ratio is a more adequate parameter to provide insight regarding sympatho/vagal balance

Table 2. *Mean and standard deviations of self-reported pain and autonomic outcome measures.*

	ME/CFS (mean ± SD)	HS (mean ± SD)	Between group comparison: ME/CFS vs HS (*P*-value)
VAS pain (muscle and/or joint pain) (mm)			
pre-exercise	50.0 ± 31.3	16.0 ± 21.2	**<.001**
post-exercise	50.0 ± 30.6	5.2 ± 7.3	**<.001**
Within group comparison: pre vs post	.423	**.001**	
VAS headache (mm)			
pre-exercise	34.5 ± 32.5	3.6 ± 7.4	**<.001**
post-exercise	39.7 ± 29.4	3.3 ± 5.5	**<.001**
Within group comparison: pre vs post	.930	.609	
SF-36 bodily pain (score)			
pre-exercise	43.5 ± 18.1	84.4 ± 14.1	**<.001**
post-exercise	45.0 ± 17.7	85.2 ± 14.6	**<.001**
Within group comparison: pre vs post	.695	.829	
HR (bpm)			
pre-exercise	71.33 ± 7.47	71.78 ± 9.78	.870
post-exercise	73.81 ± 8.56	72.59 ± 8.32	.655
Within group comparison: pre vs post	**.031**	.578	
HRV RMSSD (ms)			
pre-exercise	27.25 ± 14.70	42.51 ± 30.41	.060
post-exercise	22.32 ± 9.98	45.34 ± 29.20	**.010**
Within group comparison: pre vs post	.059	.881	
HRV LF (ms^2)			
pre-exercise	234.06 ± 240.09	470.35 ± 538.60	**.038**
post-exercise	179.03 ± 181.63	343.35 ± 286.72	**.015**
Within group comparison: pre vs post	.126	**.012**	
HRV HF (ms^2)			
pre-exercise	169.53 ±166.5	519.25 ± 772.93	.024
post-exercise	101.24 ± 81.67	513.43 ± 576.86	.001
Within group comparison: pre vs post	**.044**	.709	
HRV LF/HF ratio			
pre-exercise	1.92 ± 1.39	1.48 ± 1.20	.314
post-exercise	2.01 ± 1.21	1.33 ± 1.12	**.035**
Within group comparison: pre vs post	.841	.502	
RR (/min)			
pre-exercise	15.74 ± 4.18	17.93 ± 3.81	.656
post-exercise	17.93 ± 3.81	16.15 ± 3.23	.343
Within group comparison: pre vs post	**.003**	**.005**	
Systolic BP (mmHg)			
10 min pre-exercise	113.00 ± 12.35	110.55 ± 11.66	.523
immediate post-exercise	119.80 ± 14.59	117.55 ± 11.33	.589
10 min post-exercise	113.60 ± 12.80	113.50 ± 10.38	.979
Within group comparison: 10 min pre vs immediate post	**.001**	**.003**	
Within group comparison: 10 min pre vs 10 min post	.698	.063	
Diastolic BP (mmHg)			
10 min pre-exercise	71.10 ± 6.89	69.50 ± 8.86	.528
immediate post-exercise	72.20 ± 7.80	70.85 ± 7.82	.588
10 min post-exercise	72.45 ± 7.11	70.70 ± 7.91	.467
Within group comparison: 10 min pre vs immediate post	.262	.275	
Within group comparison: 10 min pre vs 10 min post	.183	.270	

Bold print = significant correlations ($P < .05$).

Table 3. *Correlation analyses in ME/CFS and HS group.*

		Δ	VAS pain (muscle and/or joint pain) (mm)		VAS headache (mm)		SF-36 bodily pain (score)	
			HS (post-pre) -0.8 ME/CFS (post-pre) 0.0		HS (post-pre) -0.3 ME/CFS (post-pre) 5.2		HS (post-pre) 0.8 ME/CFS (post-pre) 1.5	
			r	*P*	r	*P*	r	*P*
HR (bpm)	HS (post-pre)	0.81	-.137	.565	.011	.964	-.393	.086
	ME/CFS (post-pre)	2.48	-.190	.436	.117	.634	.257	.288
HRV RMSSD (ms)	HS (post-pre)	2.83	.127	.594	.058	.810	.063	.791
	ME/CFS (post-pre)	-4.93	.407	.084	-.357	.134	-.146	.550
HRV LF (ms^2)	HS (post-pre)	-127.00	.012	.959	.047	.845	-.102	.668
	ME/CFS (post-pre)	-55.03	**.552**	**.014**	-.038	.878	-.123	.616
HRV HF (ms^2)	HS (post-pre)	-5.82	.065	.787	.087	.715	.022	.926
	ME/CFS (post-pre)	-68.29	.226	.353	**-.480**	**.038**	-.072	.769
HRV LF/HF ratio	HS (post-pre)	-0.15	.235	.318	-.389	.090	-.028	.907
	ME/CFS (post-pre)	0.09	-.049	.841	.287	.233	.049	.842
RR (/min)	HS (post-pre)	1.78	.087	.725	.030	.903	.434	.064
	ME/CFS (post-pre)	2.19	-.169	.502	.079	.757	-.071	.778
Systolic BP (mmHg)	HS (immediate post-10 min pre)	7.00	.004	.986	.182	.444	-.089	.709
	ME/CFS (immediate post-10 min pre)	6.80	-.026	.914	.108	.650	.064	.790
	HS (10 min post-10 min pre)	2.95	.128	.589	.113	.636	-.193	.416
	ME/CFS (10 min post-10 min pre)	0.60	-.149	.532	.188	.428	.110	.645
Diastolic BP (mmHg)	HS (immediate post-10 min pre)	1.35	.246	.296	-.059	.804	.318	.172
	ME/CFS (immediate post-10 min pre)	1.10	-.261	.266	.077	.747	**.472**	**.036**
	HS (10 min post-10 min pre)	1.20	**.580**	**.007**	-.164	.491	.291	.213
	ME/CFS (10 min post-10 min pre)	1.35	-.082	.732	.049	.837	.152	.523

Bold print = significant correlations ($P < .05$).

(40) and indicated an efficient post-exertional recovery in the healthy controls. ME/CFS patients showed an impaired HR recovery and parasympathetic reactivation following exercise. We hypothesized that autonomic-mediated recovery following exercise would be associated with the magnitude of EIA. All self-reported pain measures indicated the presence of EIA in the HS group, but only the change in intensity of overall pain was large enough to reach significance, and therefore seemed the best parameter to indicate the presence of EIA in this study. This parameter remained unchanged in ME/CFS patients following exercise, indicating EIA did not occur, which is in line with previous observations (9). The possible relationship between presence or lack of EIA and autonomic functioning was explored using correlation analyses.

The impaired HR recovery following exercise was not associated with the lack of EIA in ME/CFS patients. However, the reduced parasympathetic reactivation during exercise recovery observed in ME/CFS patients was associated with a lack of EIA. These results suggest that the efficacy of autonomic recovery can possibly mediate the degree of (dys)function of EIA in ME/CFS patients.

Furthermore, the results from this study support the idea that arterial baroreceptor activity plays a role

within the phenomenon of EIA. In healthy people, the change in pain intensity in response to exercise was associated with changes in diastolic BP. A similar observation was made in ME/CFS patients, where the change in the presence of bodily pain in response to exercise was associated with post-exertional changes in diastolic BP. More specifically, a poor recovery of diastolic BP in response to exercise, with BP remaining elevated, was associated with post-exertional pain reductions, which represents EIA. It has been previously described that the arterial baroreceptors are activated by increases in BP during exercise (14-16). A poor recovery of HF following exercise, during which HF remains elevated, was associated with increased headache intensity following exercise. In addition, a poor recovery of LF, during which LF remained decreased in comparison to baseline, was associated with the lack of EIA in the muscles or joints in ME/CFS patients. The decrease of LF activity following exercise indicates that less baroreflex activity takes place during recovery from exercise than at rest, which further strengthens the theory that baroreceptor activation is a factor which determines the presence or lack of EIA.

The cardiac baroreflex sensitivity, which is the change in R-R interval per unit change in systolic BP, plays an important intermediate role between BP and pain (47). Preliminary evidence suggests reduced baroreflex sensitivity in ME/CFS patients (47), but its relationship to pain and EIA has not been studied before. Chronic pain appears to be characterized by alterations in baroreflex sensitivity as well as impairments in descending inhibitory pathways and activation of pain faciliatory pathways (48). There is some evidence that central noradrenergic changes may account for the reduced baroreceptor sensitivity associated with chronic stress (49). Therefore, the stress associated with chronic pain may lead to similar diminished baroreceptor sensitivity and thus contribute to the exaggerated pain sensitivity in ME/CFS patients (50). Furthermore, oxidative stress has been reported to modulate baroreceptor sensitivity in health and disease (51), and there are indications that the post-exertional oxidative stress response in ME/CFS occurs earlier and lasts longer (52-54). Taking this into consideration, it can be assumed that the reduced baroreflex sensitivity can be influenced by drugs which activate noradrenergic descending pathways or affect oxidative stress production. Furthermore, it has been shown that physical training causes an increase in parasympathetic tone (55) and thus could also be beneficial in ME/CFS. However, care should be taken to not elucidate pain exacerbations by carefully determining and monitoring the exercise intensity and providing sufficient long recovery periods. Unfortunately, there is currently little knowledge regarding the best exercise intensity for improving autonomic balance in ME/CFS. While drug treatments in conjunction with graded exercise therapy might be an option to improve baroreflex sensitivity and parasympathetic reactivation following exercise, which in theory would facilitate EIA to some extent, future research is necessary to examine whether this is the case.

Strengths and Limitations

Given the absence of previous data regarding the association between autonomic function during exercise recovery and EIA, an exploratory approach was used to examine this hypothesis. While this study provides indications for the role of parasympathetic and baroreflex reactivation following exercise and the presence and degree of EIA, the cross-sectional design does not allow firm conclusions regarding the causality of the observed relations. Although the sample size was limited, significant correlation coefficients ranged from 0.36 to 0.67, representing moderate associations.

Besides these limitations, this study also had several strengths. By not limiting the study to solely healthy people, but also implementing a population in which impaired EIA has been shown, we were able to detect whether subtle impairments in autonomic functioning would be related to dysfunctional EIA. On the one hand, more objective measures could have been used to assess pain (such as evaluation of pain thresholds/tolerance), but on the other hand, we assessed the endogenous effects of exercise on clinical pain which is of particular relevance for patient populations such as ME/CFS as these patients often experience post-exertional (increases of) pain complaints following daily physical activities. Both studied populations were well matched regarding gender, age, body mass index, and exercise capacity, so that these factors could not be explanatory for the differential group findings. Furthermore, we anticipated different potential sources of bias on the days of the assessment. A final strength is that all measures took place in an acclimatized room, which is required for valid exercise and autonomic measurements.

Conclusion

Reduced parasympathetic reactivation during recovery from exercise is associated with the dysfunctional EIA in ME/CFS. In addition, poor recovery of diastolic BP

in response to exercise, with BP remaining elevated, is associated with reductions of pain following exercise in ME/CFS, suggesting a role for the arterial baroreceptors in explaining dysfunctional EIA in ME/CFS. Unravelling the mechanisms responsible for the dysfunctional EIA in response to exercise in people with ME/CFS is likely to be a crucial step towards treatment.

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Conflict of interest

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